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Combination of RAF and MEK Inhibition for the Treatment of BRAF-Mutated Melanoma: Feedback Is Not Encouraged

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In BRAF V600E melanoma patients, RAF inhibitor treatment causes a MEK-inhibitor-sensitive, RAF-inhibitor-resistant adaptive reactivation of ERK signaling. In clinical trials combining MEK and RAF inhibitors, therapeutic efficacy was modestly enhanced, suggesting the utility of inhibiting feedback-reactivated pathways. Strategies for optimally inhibiting ERK signaling should be explored.

The RAS/RAF/MEK/ERK pathway is dysregulated in almost all melanomas, mostly due to activating mutations of BRAF or NRAS or genetic changes causing loss of NF1 function. Inhibitors of this pathway have attracted a great deal of interest as therapeutics. Potent (>80%) inhibition of ERK signaling is required for significant antitumor activity (Bollag et al., 2010). MEK inhibitors have only modest clinical activity in these patients (Flaherty et al., 2012), perhaps because MEK inhibitors suppress ERK signaling in both tumor and normal cells; thus, on-target toxicities limit the doses that can be administered safely. This is not the case for RAF inhibitors. They selectively inhibit ERK signaling in melanomas that express the most common RAF mutations (BRAF V600E/K), whereas they induce ERK signaling in normal and other tumor cells. This paradoxical activation of ERK is due to transactivation of wild-type RAF dimers when one protomer of the dimer is bound to drug (Poulikakos et al., 2010). In most melanomas, BRAF V600E exists as a monomer and is inhibited potently by drug (Poulikakos et al., 2011).

Tumor- and mutation-specific inhibition of ERK signaling by RAF inhibitors explains their broad therapeutic index. The two Food and Drug Administration (FDA)-approved RAF inhibitors—vemurafenib and dabrafenib—have high response rates in BRAF-mutated melanomas (approximately 50%), and vemurafenib improves patient survival (Chapman et al., 2011; Hauschild et al., 2012). However, antitumor responses are usually temporary and rarely complete. Treatment is also complicated by toxicities attributable to ERK activation in skin, including hypertrophic skin changes and induction of keratoacanthomas and cutaneous squamous cell carcinomas.

Inhibition of ERK signaling in BRAF mutant tumors relieves ERK-dependent feedback inhibition of receptor signaling and of CRAF kinase activity. This results in induction of RAS activation, formation of RAF inhibitor-resistant, wild-type CRAF dimers, and a rebound in ERK activation that is sensitive to MEK inhibitors but resistant to RAF inhibitors (Lito et al., 2012). These results imply that the adaptive rebound in ERK signaling in tumors exposed to RAF inhibitors may reduce their clinical effectiveness. Addition of MEK inhibitors might therefore reduce the toxicity (by antagonizing the paradoxical activation of ERK in normal cells) and enhance the effectiveness of RAF inhibitors (by further inhibiting ERK in tumor cells). Two such

trials have recently been reported that test this hypothesis (Larkin et al., 2014; Long et al., 2014). In each, previously untreated patients with metastatic BRAF-mutated melanoma were randomly assigned to treatment with RAF inhibitor monotherapy or a RAF inhibitor plus a MEK inhibitor.

In the trial of Long and colleagues, patients were treated with either dabrafenib alone (150 mg twice daily) or dabrafenib combined with trametinib (2 mg daily). Earlier in the year, the FDA granted accelerated approval of this combination based on a small randomized phase II trial in which, compared to dabrafenib monotherapy, the combination doubled the complete response rate (4% versus 9%) and improved median progression-free survival by 16 weeks (5.8 to 9.4 months) (Flaherty et al., 2012). The results of the trial by Long and colleagues, designed as a large (423 patients) confirmatory study, were disappointing. The combination did not increase the rate of complete responses and prolonged median progression-free survival by only 2 weeks. Follow-up has been too short to assess overall survival, although there is a trend in favor of the combination. The addition of the MEK inhibitor decreased toxicities thought to result from RAF-inhibitor-induced activation of the ERK pathway (hyperkeratosis and squamous cell carcinomas of the skin). However, other toxicities, such as fever and diarrhea, were more common in patients treated with the combination and led to discontinuance of treatment in 9% of patients on the combination arm compared to 5% receiving dabrafenib monotherapy.

The other phase III trial, Larkin et al. (2014), randomly assigned 495 previously untreated patients with BRAF-mutated melanoma to a different RAF inhibitor (vemurafenib 960 mg twice daily) alone or in combination with a different MEK inhibitor (cobemetinib 60 mg daily for 21 days followed by 7 days off). The vemurafenib/cobimetinib combination induced more complete responses than vemurafenib alone (10% versus 4%). The combination also improved median progression-free survival (9.9 months versus 6.2 months), a difference of 16 weeks. As with the trial by Long and colleagues, the RAF/MEK inhibitor combination was associated with less skin toxicity but with more fever, diarrhea, and retinal changes (mostly asymptomatic). Also, consistent with the study by Long et al., a trend toward improved survival was observed with the combination.

In each of the two trials, treatment with the MEK and RAF inhibitor combination was associated with a median progression-free survival of 9–10 months. In both trials, this was statistically superior to the RAF inhibitor alone, although in the case of dabrafenib/trametinib, there was only a 2 week difference. It is possible that at the doses used, a higher degree of MEK inhibition was obtained with cobimetinib than with trametinib, thus resulting in the greater improvement over RAF inhibitor monotherapy. In any event, drug resistance remains a major clinical problem even with the addition of a MEK inhibitor. The mechanisms of resistance were not reported in these papers, although other recent work shows that resistance to combined inhibition of MEK and RAS is typically associated with ERK reactivation similar to what is observed with RAF inhibitor monotherapy (Wagle et al., 2014).

Many questions remain unanswered concerning the mechanisms underlying these clinical responses and how to enhance them. The results reflect an improvement in outcome, but median time to progression is still less than 1 year. The best RAF and MEK inhibitors (or potentially ERK inhibitors) to use and the optimal dosage and schedules remain unknown. The pharmacologic and biochemical properties of these drugs vary, and it has been recently shown that the antitumor effects of some MEK inhibitors are less sensitive to feedback reactivation of CRAF. Intermittent therapy with a RAF inhibitor has also recently been shown to be more effective than daily scheduling in treating BRAF V600E tumors in a PDX model (Das Thakur et al., 2013) and could allow higher doses of MEK inhibitor.

These trials showed that the toxicity of RAF inhibitors caused by paradoxical pathway activation in normal cells can be blocked by MEK inhibition. Other RAF inhibitor toxicities, such as fever and gastrointestinal toxicities, were more frequent in patients receiving combination therapy. It is not known whether these toxicities can be minimized by altering the dosing of each drug to balance the inhibition and paradoxical activation of ERK induced by the MEK and RAF inhibitors, respectively, or whether some of these are off-target toxicities. MEK inhibitors have other class-specific reversible toxicities, such as rash, retinopathy, and myocyte damage. There is reason to suspect that pathway activation by RAF inhibitors in these tissues could reduce these toxicities, allowing for the administration of higher doses of MEK inhibitors. Understanding the mechanisms by which this combination works, using pharmacologic principles and drugs with superior biochemical properties to maximize pathway inhibition and minimize or inhibit adaptive responses, could lead to considerable improvement in the therapeutic effects of this regimen.

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